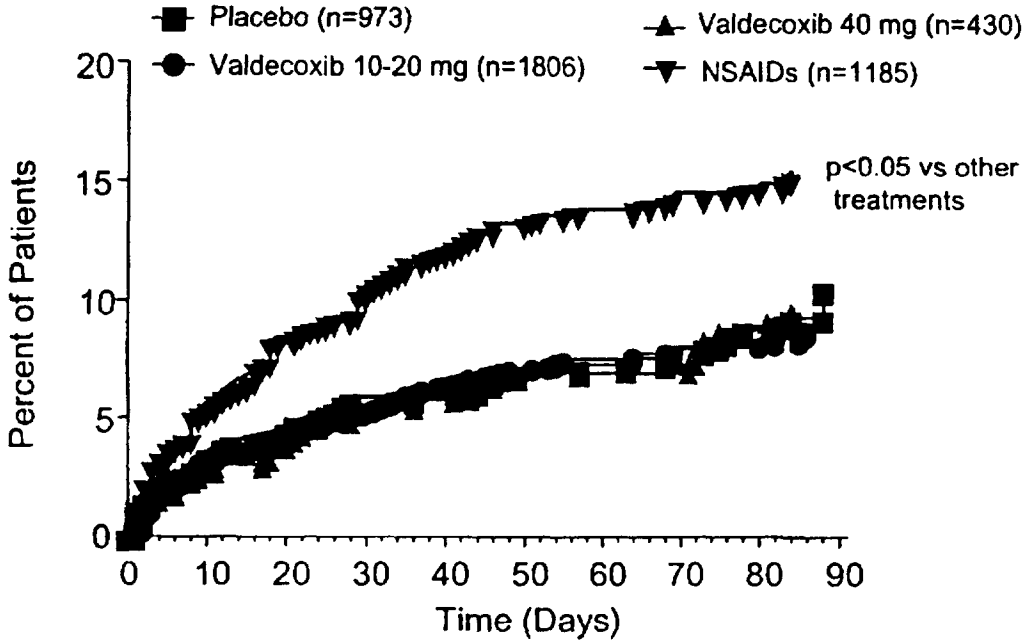
such short-term drug exposure studies are evanescent and not linked to clinical sequelae. Consequently, results from these bioassays are of uncertain clinical relevance.

Upper GI Endoscopy Studies in Arthritis Patients

Three randomized, double-blind endoscopy studies (studies 048, 053 and 047) were performed in patients with OA or RA treated with valdecoxib or a non-selective NSAID (see Table 3). Study 048 and 053 were 12 week trials which included a placebo group whereas study 047 was a 26 week active control study only. In the placebo controlled studies each of the valdecoxib treatment arms as well as the non-selective NSAID and placebo treatment arms consisted of approximately 200 patients that originated from more than 80 study sites. Subjects were excluded from the studies if they had greater than 10 gastric/duodenal erosions or gastroduodenal ulcers at pre-treatment endoscopy. The 200 patient per treatment group sample size was calculated to be sufficient to detect differences between gastroduodenal ulcer rates of 5% in the valdecoxib treatment group and 16% or larger in the comparative NSAID groups with a power of 80% and a 0.017 level of significance. In study 048 the active comparator non-selective NSAID treatment arms were ibuprofen 800 mg TID and diclofenac 75 mg BID, whereas in Studies 047 and 053 the active comparator was naproxen 500 mg BID. Confounding risk factors for gastroduodenal ulceration in subjects enrolled in studies 048 and 053 are shown in Table 14.g. In the 10 mg of the valdecoxib treatment arm of Study 048 there were only nine low dose ASA users whereas in the other active treatment arms the numbers of low dose ASA users ranged between 16 and 18. Similarly, in study 053 in the 5 mg valdecoxib treatment arm only 37 patients manifested *H. pylori* positive serology whereas in the non-selective NSAID treatment arm 43 patients were serologically positive. In addition, in the 5 mg valdecoxib treatment arm, 10 patients had a history of GDU whereas in the non-selective NSAID treatment arm 15 patients had a history of ulcers. Although these differences are modest they have the potential of impacting on small differences in the rates of ulcer complications linked to these studies. Figure 1 shows the GDU rates in the valdecoxib and non-selective NSAID treatment arms in studies 048 and 053. Although in both studies statistical differences were noted in ulcer rates between the non-selective NSAID treatment arms and the 10 mg valdecoxib treatment arm in study 053 a statistical difference between the naproxen treatment arm and the valdecoxib 20 mg treatment arm was not achieved. (Nonetheless, the non-selective NSAID was associated with a higher incidence of gastroduodenal ulcers; see Figure 3).

Figure 3



• moderate to severe abdominal pain, dyspepsia, nausea

As in the case of the short-term bioassays the duodenal ulcer rates were small compared to the gastric ulcer rates in all the patient studies. It should be emphasized that in studies 048 and 053 the highest dose of valdecoxib that was tested was 20 mg which is the currently recommended dose for treatment of osteoarthritis and adult rheumatoid arthritis in the proposed draft labeling. However, a higher dose of 40 mg is recommended for other conditions including management of acute pain, pre-operative dosing and primary dysmenorrhea. This higher dose was used in one of the treatment arms of study 047 which was a randomized, double-blind, parallel group, multi-center 26 week study of valdecoxib 20 and 40 mg BID treatment arms with an active non-selective NSAID comparator (naproxen 500 mg BID). All patients had a pre-treatment endoscopy and a follow-up endoscopy at week 14 of treatment. Approximately 400 patients were randomized into each treatment arm. The incidences of confounding risk factors for the development of gastroduodenal ulceration for patients enrolled in study 047 are shown in Table 6.

TABLE 6

Demographics, Medical History, Baseline *H. pylori* Status, and Aspirin Use: Study 047

	Valdecoxib 20 mg BID (N=399)	Valdecoxib 40 mg BID (N=404)	Naproxen 500 BID (N=415)
Mean Age (yrs)	56.2	56.1	55.8
Female	72	72	71
RA patients	49	51	51
Age ≥ 65 years	27	29	23
Age ≥ 75 years	7	7	4
History of GI Bleeding	2	2	2
History of Gastroduodenal Ulcer	11	10	11
History of Cardiovascular Disease	45	46	45
H. Pylori Positive Serology	25	26	32
Aspirin Use (≤325 mg/day)	14	11	14

Entries are % of patients except mean age
Derived from individual Final Study Report

It is apparent that the naproxen 500 mg BID treatment arm contained a slightly higher number of patients who were serologically positive for *H. pylori* compared to the valdecoxib treatment arms (32 vs 25 and 26). Nonetheless, the baseline risks for complicated GDUs appear to be well balanced between all treatment arms. In study 047 over the 14 week treatment period the incidence of GDUs were statistically significantly lower in valdecoxib treated patients for both doses of valdecoxib (20 mg and 40 mg BID) compared to patients receiving naproxen (see Table 7).

TABLE 7

Ulcer Incidence Rates: High-Dose OA and RA Safety Trial

	Valdecoxib 20 mg BID (N=399)	Valdecoxib 40 mg BID (N=404)	Naproxen 500 mg BID (N=415)
Gastroduodenal			
All Patients	6% (14/253)	9% (24/259)	23% (63/272)*
RA Patients	7% (9/127)	7% (10/135)	20% (29/143)*
OA Patients	4% (5/126)	11% (14/124)**	26% (34/129)*
Gastric			
All Patients	4% (9/249)	8% (20/258)	18% (49/265)*
RA Patients	4% (5/124)	6% (8/135)	18% (25/140)*
OA Patients	3% (4/125)	10% (12/123)**	19% (24/125)*
Duodenal			
All Patients	2% (6/252)	2% (5/257)	7% (19/267)*
RA Patients	3% (4/126)	1% (2/134)	4% (6/139)*
OA Patients	2% (2/126)	2% (3/123)	10% (13/128)*

* Significantly different from both valdecoxib treatments; $p<0.05$.
** Significantly different from valdecoxib 20 mg BID; $p<0.05$
Entries are % of patients with ulcer (No. with ulcer/ No. with known result). Known endoscopy results include an ulcer detected at any time, or a finding of no ulcer at an endoscopy performed at 98 ±7 days.
Derived from individual Final Study Report.

It should be noted that significantly higher incidences of GDUs were observed with valdecoxib 40 mg BID in osteoarthritis patients when compared to 20 mg BID. Therefore, it appears that although valdecoxib at both 20 mg BID and 40 mg BID doses were associated with lower ulcer incidence rates compared to naproxen there was a dose related effect on ulcer incidence associated with the COX-2 inhibitor. Once again, differences in duodenal ulcer rates between the non-selective NSAID comparator and each of the valdecoxib treatment arms were comparatively small (7% vs 2% for all patients entered in the study). Moreover, no differences in duodenal ulcer incidence was noted between each of the valdecoxib treatment arms.

In study 047 (see Table 8), both low dose ASA use and elderly age (≥65 years) were linked to higher GDU rates in valdecoxib users (both 20 mg BID and 40 mg BID doses). In addition, a history of GDUs was associated with increased risk for GDUs in the valdecoxib 40 mg treatment arm.

TABLE 8

Effect of Demographic Covariates and Potential Risk Factors on Gastrointestinal Ulcer Incidence Rates: Study 047

	Valdecoxib 20 mg BID	Valdecoxib 40 mg BID	Naproxen 500 mg BID
Low dose Aspirin (≤325 mg/day) Use			
Users	12% (6/49)	26% (10/38)*	13% (7/54)
Nonusers	3% (9/296)	5% (17/317)	19%(59/310)
Age			
≥ 65 years	8% (8/99)*	14% (15/107)*	27% (24/88)*
< 65 years	3% (7/246)	5% (23/248)	15% (42/276)
***H. pylori* status (CLOtest)**			
Positive	7% (4/61)	10% (7/71)	25% (19/76)
Negative	4% (10/230)	9% (19/215)	19% (43/232)
History of Gastroduodenal Ulcer			
History	8% (3/36)	28% (10/36)*	37% (16/43)*
No History	4% (12/309)	5% (17/319)	16% (50/321)

* Significant within treatment difference; p=<0.05.
Enteries are % of patients with ulcer (No. with ulcer/No. with posttreatment endoscopy) at first visit.
Derived from individual Final Study Report

These results point to an interplay between other risk factors and the potential to develop GDUs in specialized patients being treated with valdecoxib. The results underline the need for adequately powered studies to measure the risk to develop GDUs associated with valdecoxib use for 3 months or longer in each of the aforementioned subsets of the population.

Clinically Significant Upper GI Events in Arthritis Studies

Clinically significant upper GI events of pooled data across multiple valdecoxib arthritis studies were analyzed (Study 803). The pooled analysis incorporated studies in which the comparator nonselective NSAID treatment arms consisted of naproxen 500 mg BID, diclofenac 75 mg BID

or ibuprofen 800 mg TID. The clinically significant upper GI events that were scored were a composite endpoint comprised of bleeding, perforation or gastric outlet obstruction events. The analysis encompassed data from 6 controlled valdecoxib arthritis studies (studies 047, 048, 049, 053, 060 and 061) and three long-term open label trials (studies 031, 067 and 076). The durations of exposure to valdecoxib in these studies ranged between 12 weeks and one year. Asymptomatic ulcers identified during scheduled endoscopies by investigators were not scored as significant events for the purpose of this analysis. Members of a full Gastrointestinal Events Committee who were blinded to both studies as well as treatment assignment adjudicated each case submitted to the sponsor by consensus in order to determine, by prespecified criteria, whether a clinically significant upper GI event had occurred. The criteria for each category of significant upper GI events were:

1. Upper GI bleeding associated with a gastric or duodenal ulcer or large erosion proven by endoscopy or upper GI barium X-ray linked to one of the following 7 clinical presentations:

- Hematemesis
- Active bleeding or stigmata of a recent hemorrhage identified endoscopically
- Melena
- Hemoccult positive stools and a fall in hematocrit of $\geq$5% points or a reduction of globulin $\geq$1.15 g/dL.
- Hemoccult positive stools with orthostasis
- Hemoccult positive stools associated with blood transfusions of 2 or more units
- Hemoccult positive stools associated with blood in the stomach determined by nasogastric aspiration or endoscopy

2. Upper GI perforation evidenced by unequivocal findings/signs

3. Gastric outlet obstruction based on endoscopic and/or upper GI barium X-ray evidence.

An analysis of the composite of the upper GI events in study 803 was performed by calculation of crude and Kaplan-Meier rates of events of occurrence by time interval and comparisons between treatment groups were analyzed by log-rank test. A similar analysis of clinically significant upper GI events combined with symptomatic ulcers was performed. Symptomatic ulcers were defined as gastroduodenal ulcers first were detected after presentation of a gastrointestinal sign or symptom either during unscheduled or scheduled endoscopies. Ulcers were defined as breaks in the mucosa $\geq$3 mm with unequovical depth documented either by endoscopy or barium X-ray. A separate analysis was performed on the subset of patients concomitantly treated with low dose aspirin ($\leq$325 mg/day).

A total of 5,932 patients enrolled in the 12 to 16 week controlled arthritis trials (studies 047, 048, 049, 053, 060 and 061) received at least one dose of medication (NSAID or placebo). The demographic characteristics of patient enrolles are shown in Table 9.

TABLE 9

Patient Demographics, Medical History and Concurrent Medications: 12- to 26-Week Controlled Arthritis Trials

Characteristic	Placebo (n=973)	Valdecoxib 5-80 mg/day (n = 3359)	NSAIDs (n = 1600)
Mean age (range), y	58.8 (19-88)	57.2 (19-90)	59.4 (18-88)
≥65 years of age (%)	35	30	32
≥75 years of age (%)	9	8	9
Women, (%)	71	72	71
Race, (%)			
White	81	80	81
Black	8	9	10
Hispanic	10	9	7
Asian	0	1	1
Other	1	1	1
Primary disease, (%)			
RA	45	51	41
Potential Risk Factor (%)			
History of GI bleeding	1	1	2
History of GI ulcer	10	11	12
Positive *Helicobacter pylori* serology (%)	16	19	25
Test not performed	57	46	35
Concurrent medications, (%)			
Aspirin (≤325 mg daily)	13	14	15
Corticosteroids	20	24	20

Data derived from Tables T4, T5 and T6, Study 803 final report

From this Table it is apparent that information about *H. pylori* serological status in all patients was not available. As alluded to above positive serology does not necessarily indicate active *H. pylori* infection. Therefore positive serology does not identify with high specificity individuals who may be at increased risk for the development of gastroduodenal ulcers. The analysis of study participants in the valdecoxib treatment arms of the combined studies includes individuals treated with a range of doses of valdecoxib. Some study subjects were treated with doses that are subtherapeutic. In contrast, in the nonselective NSAID treatment arms doses were in the high therapeutic range. Therefore, comparability of safety event outcomes between the COX-2 inhibitor treatment arms and the nonselective NSAID arms is difficult to assess because of the absence of absolute dose equivalence.

The wide rate of clinically significant upper GI events was 0.58% (7 cases/1,197 treated subjects). Although in study 048 the numbers of subjects treated with ibuprofen and diclofenac

were too small to determine whether these rates were similar to the rate associated with naproxen treatment in the CLASS study it is likely that they are lower and closer to those associated with valdecoxib treatment.

In the composite of controlled arthritis studies in which the non-selective NSAID presentation is heavily weighted in the number of subjects treated with naproxen 500 mg BID compared to ibuprofen 800 mg TID and diclofenac 75 mg BID (n=1,181, n=207 and n=212, respectively; sponsor's Table T1).

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Table T1
Patient Disposition by Study and Treatment

Intent-to-Treat Cohort

	PLACEBO	VALDECOXIB 5 mg QD	VALDECOXIB 10 mg QD	VALDECOXIB 20 mg QD	VALDECOXIB 20 mg BID	VALDECOXIB 40 mg QD	VALDECOXIB 40 mg BID	NAPROXEN 500 mg BID	IBUPROFEN 800 mg TID	DICLOFENAC 75 mg BID
RANDOMIZED CONTROLLED STUDIES										
N91-98-02-048	209		204	219					207	212
N91-99-02-047					399		403	415		
N91-99-02-049	117	120	111					118		
N91-99-02-053	205	201	205	201				204		
N91-99-02-060	222		209	212		221		225		
N91-99-02-061	220		226	219		209		219		
TOTAL	973	321	955	851	399	430	403	1181	207	212

Consistent with findings of the CLASS study, a reduction of incidence of clinically significant upper GI events was apparent only in non-ASA users treated with valdecoxib compared to the non-selective NSAID treatment arms. This difference was not apparent in ASA users (0.07% vs 0.5% and 0.6% and 0.0%) see sponsor's Table T12.

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Table T12
Risk Factor Analysis of Clinically Significant UGI Events
Randomized Controlled Studies

Intent-to-Treat (ITT) Cohort

	PLACEBO (N = 973)	VALDECOXIB (N = 3359)	NSAIDS (N = 1600)	P-Value (a) Treatment by Factor Interaction	P-Value (a) Factor Effect
AGE (years)					
<75	0/ 890(0.0%)	4/3101(0.1%)	6/1464(0.4%)	0.796	0.294
>=75	0/ 83(0.0%)	1/ 258(0.4%)	1/ 136(0.7%)		
P-VALUE(b)		0.309	0.529		
GENDER					
MALE	0/ 286(0.0%)	1/ 950(0.1%)	3/ 465(0.6%)	0.421	0.733
FEMALE	0/ 687(0.0%)	4/2409(0.2%)	4/1135(0.4%)		
P-VALUE(b)		0.677	0.427		
DISEASE TYPE					
OA	0/ 531(0.0%)	4/1662(0.2%)	4/ 943(0.4%)	0.283	0.436
RA	0/ 442(0.0%)	1/1697(<0.1%)	3/ 657(0.5%)		
P-VALUE(b)		0.243	0.913		
ASPIRIN USE					
ANY	0/ 126(0.0%)	3/ 477(0.6%)	0/ 242(0.0%)	0.007	0.394
NONE	0/ 847(0.0%)	2/2882(<0.1%)	7/1358(0.5%)		
P-VALUE(b)		0.017	0.993		
HISTORY OF CARDIOVASCULAR DISEASE					
YES	0/ 457(0.0%)	4/1571(0.3%)	5/ 780(0.6%)	0.685	0.048
NO	0/ 516(0.0%)	1/1788(<0.1%)	2/ 820(0.2%)		
P-VALUE(b)		0.159	0.237		
HISTORY OF UPPER GI BLEEDING					
YES	0/ 13(0.0%)	0/ 42(0.0%)	1/ 31(3.2%)	0.361	0.179
NO	0/ 960(0.0%)	5/3317(0.2%)	6/1569(0.4%)		
P-VALUE(b)		0.994	0.043		
HISTORY OF GASTRODUODENAL ULCER					
YES	0/ 100(0.0%)	3/ 352(0.9%)	2/ 195(1.0%)	0.233	0.006
NO	0/ 873(0.0%)	2/3007(<0.1%)	5/1405(0.4%)		
P-VALUE(b)		0.005	0.184		

(a) Based on survival analysis on the time to UGI events with a COX proportional hazards model.
(b) Within group survival analysis on the time to UGI events with a COX proportional hazards model.

In these valdecoxib randomized controlled studies in ASA users there was an unexpected absence of cases of clinically significant upper GI events among non-selective NSAID users, whereas the concomitant use of valdecoxib and aspirin was associated with an incidence of 0.6%. Therefore, the use of aspirin caused an increase in risk for clinically significant upper GI events between 8 and 9 fold only in patients treated with valdecoxib. Importantly, in addition to the use of the low dose ASA, a history of GDU was associated with a 13 to 14 fold increase in risk for the development of clinically significant upper GI events in patients treated with valdecoxib. This increase in risk was greater than that identified for non-selective NSAID users (2.5 fold increased risk). From these data certain subsets of patients who at baseline are at increased risk to develop clinically significant upper GI events (including those who are aspirin users and who have a history of GDU) are particularly prone to develop complications when treated with valdecoxib.

Further Information About Clinically Significant Upper GI Events in 12 to 26 Week Controlled Arthritis Trials

The Gastrointestinal Events Committee adjudicated 211 potential clinically significant upper GI events in the 12/26 week controlled arthritis trials. A flow-chart of the patient categorizations determined by the Committee is shown in Figure 4.

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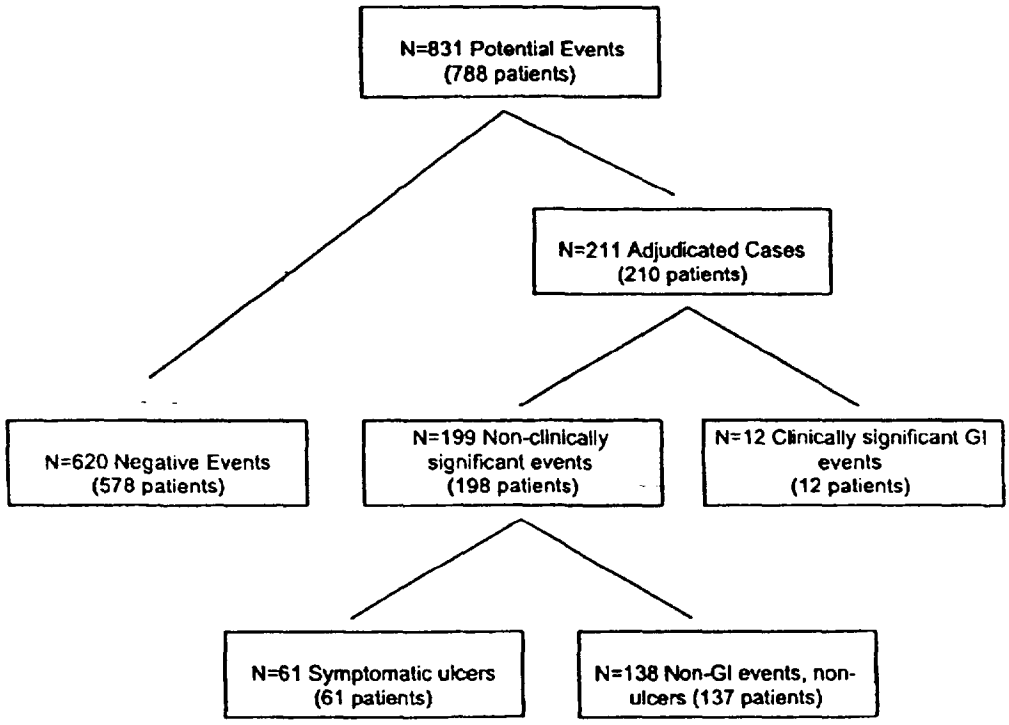
Figure 4

Disposition of Potential Clinically Significant UGI Events – 12- to 26-Week Controlled Arthritis Trials



It is apparent that of the adjudicated cases 5 patients treated with valdecoxib (5 to 80 mg doses; n=3,359) were judged to be clinically significant upper GI events and 22 cases symptomatic GDUs. All five of the clinically significant events were associated with upper GI bleeding (see Table 10)

TABLE 10

Number of Adjudicated Cases and Adjudicated Cases Meeting Pre-Specified Definitions of Clinically Significant Upper GI Events and Symptomatic Gastroduodenal Ulcers: 12- to 26-Week Controlled Arthritis Trials

Category	Placebo (n=973)	Valdecoxib 5-80 mg (n = 3359)	NSAIDs (n = 1600)
Total cases adjudicated	21	96	94
Adjudicated cases not meeting the definition of a clinically significant upper GI event or symptomatic gastroduodenal ulcer	19	69	50
Esophageal disease	4	11	13
Gastroduodenitis	3	13	18
Colonic or small bowel disease	2	3	2
Non-ulcer bleeding	2	16	3
Non-specific GI symptoms	4	21	9
Anemia	1	2	2
Miscellaneous	3	3	3
Adjudicated cases meeting the definition of a gastroduodenal ulcer or clinically significant upper GI event	2	27	44
Symptomatic gastroduodenal ulcers	2	22	37
Clinically Significant Upper GI Events	0	5	7
Upper GI bleeding	0	5	7
Perforation	0	0	0
Gastric outlet obstruction	0	0	0

Derived from Study 803 final report.

Endoscopic findings associated with these cases are summarized in Table 11.

TABLE 11

Distributions of Clinically Significant UGI Events by Treatment Group and Category: 12- to 26-Week Controlled Arthritis Trials

Event Category	Valdecoxib 10 mg TDD (N=966)	Valdecoxib 40 mg TDD (N=845)	Valdecoxib 80 mg TDD (N=420)	Naproxen 500 mg BID (N=1197)
UGI Bleeding (Category 1)				
1A: Hematemesis with ulcer/large erosion	-	-	-	2
1B: Ulcer/large erosion with evidence of bleeding	-	-	1	4
1C: Melena with ulcer/large erosion	-	1	-	1
1D-1: Hemoccult-positive stool with ulcer/large erosion and hematocrit/hemoglobin drop	1	1	1	-
1D-2: Hemoccult-positive stool with ulcer/large erosion and orthostasis	-	-	-	-
1D-3: Hemoccult-positive stool with ulcer/large erosion and transfusion	-	-	-	-
1D-4: Hemoccult-positive stool with ulcer/large erosion and blood in stomach	-	-	-	-
UGI Perforation (Category 2)	-	-	-	-
Gastric Outlet Obstruction (Category 3)	-	-	-	-
Total	1	2	2	7

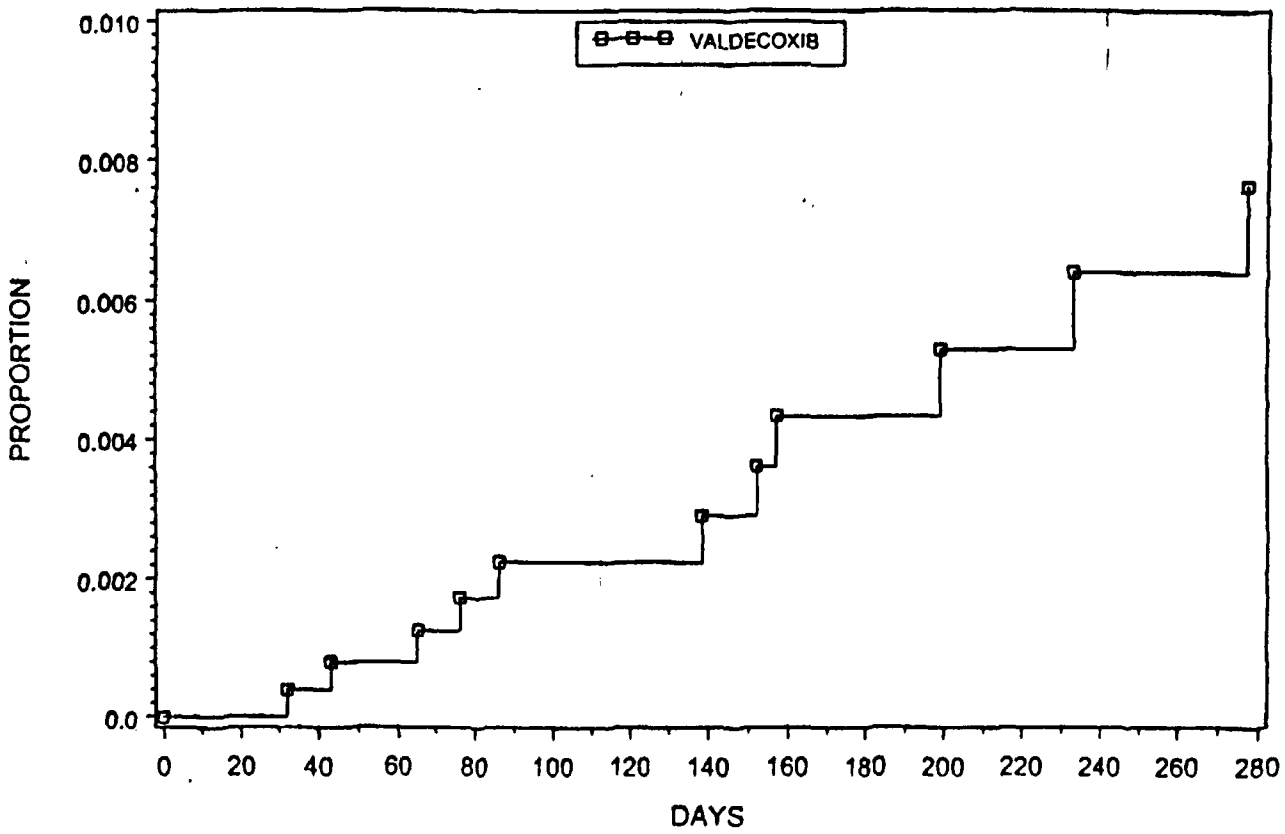
Derived from Study 803 final report. Entries are numbers of patients.

Significant ulcerated lesions associated with GI bleeding were observed in all valdecoxib dose groups (10 mg to 80 mg per day). No perforations or gastric outlet obstructions were observed. Narratives of the five cases of clinically significant upper GI bleeding associated with valdecoxib treatment are provided in Appendix 1.

From these case histories it is apparent that adaptation to long-term treatment with valdecoxib with an associated plateau in a time dependent risk to develop clinically significant upper GI events and symptomatic ulcers was not observed (see sponsor's Table T37).

Time to Clinically Significant UGI Events and Symptomatic Ulcers
Long Term Open Label Studies
Log-Rank Test

Intent-to-Treat (ITT) Cohort



Long-Term Open Label Arthritis Studies

A total of 2,867 patients were enrolled in studies 031, 067 and 076. These patients received at least one dose of valdecoxib ranging between 10 and 80 mg daily. Their demographic characteristics are shown in Table 12.

TABLE 12

Patient Demographics, Medical History and Concurrent Medications: Long-term Open Label Arthritis Trials

Characteristic	Valdecoxib 10-80 mg/day (n = 2867)
Mean age (range), y	59.2 (18-92)
≥65 years of age (%)	36
≥75 years of age (%)	10
Women, (%)	72
Race, (%)	
White	88
Black	6
Hispanic	4
Asian	1
Other	1
Primary disease, (%)	
RA	52
Potential Risk Factor (%)	
History of GI bleeding	2
History of GI ulcer	10
Positive *Helicobacter pylori* serology (%)	
Test not performed	100
Concurrent medications, (%)	
Aspirin (≤325 mg daily)	16
Corticosteroids	31

Data derived from Tables T24, 25 and 26, Study 803 *final report*

It is apparent that over a third of the valdecoxib treated individuals were in the geriatric age range. Moreover, 10% of the treated patients had a history of GI ulcer and 16% were concomitantly treated with ASA. In these studies patients were not screened for *Helicobacter pylori* serological status. Adjudication by the Gastrointestinal Events Committee identified five clinically significant upper GI events in conjunction with seven symptomatic ulcers. Based on a composite of 1,352 patient years the annualized incidence of clinically significant upper GI events in valdecoxib treated patients in these long-term open label trials was 0.37%. A limitation of this analysis is that of the 2,867 patients who were tracked in the study only 41% were treated for longer than 26 weeks and 20% were treated for less than 8 weeks. Thus, although in the total group there were 1,352 accumulated patient years, the duration of drug exposure varied considerably. Therefore, the actual risk to develop clinically significant upper GI events in individuals treated for 26 weeks or longer was probably underestimated.

Not surprisingly, low dose ASA was found to exert a statistically significant effect ($p<0.001$) on the incidence of clinically significant upper GI events in symptomatic ulcers in the long-term open label trials. The annualized incidence of clinically significant upper GI events plus symptomatic ulcers linked to valdecoxib tretment was 0.89%. In the non-aspirin users subset this incidence was 0.36%. The sponsor has attributed the lower annualized incidence rates of these events in the long-term open label trials compared to the 26 week controlled arthritis trials to the absence of scheduled endoscopies.

GI Tolerability of Valdecoxib

As shown in Table 13 certain common adverse events in the valdecoxib treatment arms of the controlled arthritis trials appear to be dose related (daily dose range between 1 and 40 mg). These include abdominal pain, nausea, flatulence, abdominal fullness and constipation. .

TABLE 13
Gastrointestinal Adverse Events with Incidence ≥3% in Any Treatment Group: Controlled Arthritis Trials

		Valdecoxib (Total Daily Dose)				
Adverse Event	Placebo	1-5 mg	10 mg	20 mg	40 mg	NSAIDs
No. treated	1142	818	1284	1012	430	1347
Dyspepsia	5.8	7.2	7.7	7.4	8.4	12.0
Abdominal pain	5.7	5.4	6.2	6.6	9.1	10.1
Nausea	5.9	5.9	6.9	6.2	7.4	7.9
Diarrhea	4.1	4.2	5.4	5.5	6.0	6.2
Flatulence	3.5	2.4	3.0	4.1	4.0	5.3
Abdominal fullness	1.7	1.2	1.9	2.2	3.3	2.7
Constipation	1.6	1.5	1.3	1.7	2.1	5.1

Derived from Table T30.1.2. All entries are percentages of patients unless otherwise specified.

Moreover, at 40 mg doses the incidence rates of abdominal pain and stomatitis were significantly higher in valdecoxib treated patients than the patients treated with placebo (see Table 14).

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TABLE 14

Analysis of GI Adverse Events between Valdecoxib (40 mg TDD) and Placebo or Active Control: Controlled Arthritis Trials

Adverse Event	Valdecoxib*	Placebo	NSAIDs	Valdecoxib vs Placebo	Valdecoxib vs NSAIDs
No. treated	430	442	444	-	-
Abdominal pain	9.1	5.0	9.0	0.023	-
Constipation	2.1	2.3	4.7	-	0.040
Stomatitis	1.9	0.0	1.1	0.003	-

Derived from Table T6.3.2. Data are expressed in percentages of patients (except for p-values), and include any events with ≥1% incidence in any group and a statistically significant difference ($p \leq 0.05$) between valdecoxib and either placebo or active control.
*Column includes only valdecoxib 40 mg TDD.

Nonetheless, the incidences of these symptoms were lower than those associated in the non-selective NSAID control patients, most of whom were treated with naproxen 500 mg BID. In the general surgery trials significant differences in rates of abdominal pain, constipation, nausea and vomiting were not noted between the valdecoxib 20 to 40 mg treatment groups and those treated with non-selective NSAIDs. In contrast, patients treated with oxycodone developed constipation, nausea and vomiting at significantly higher rates (Table 15).

TABLE 15

Analysis of Common GI Adverse Events: [redacted] Trials

Adverse Event	Valdecoxib 20-40 mg	Oxycodone/ APAP	P value	Valdecoxib 20-40 mg	NSAIDs	P value
No. treated	337	250		408	203	
Abdominal pain	6.8	7.6	-	5.4	6.9	-
Constipation	5.6	10.4	0.041	6.4	4.9	-
Nausea	17.5	28.4	0.002	14.2	19.7	-
Vomiting	8.3	16.4	0.004	7.6	6.4	-

Derived from Tables T11.3.2 and T11.3.3. Includes Studies 010, 011, 032, 033, 037, 052, and 072. *All entries are percentages of patients unless otherwise specified.*
Data are expressed in percentages of patients (except for p-values).

In summary

- In the 10 to 20 mg daily dose range valdecoxib treatment was associated with a statistically significant lower incidence of dyspepsia, abdominal pain, and constipation.
- At higher daily doses (40 mg — 80 mg) differences in the incidences of these adverse events in the controlled arthritis trials diminished and are not statistically significant (see Table 13).
- In the [redacted] trial patients subpopulation, differences in the rates of common GI adverse events (abdominal pain, constipation, nausea and vomiting) between the valdecoxib 20 to 40 mg treatment groups and non-selective NSAIDs were not apparent.

- An analysis of GI adverse events causing withdrawal between valdecoxib treatment and the non-selective NSAID comparator groups revealed a small but statistically significant difference in the incidence of abdominal pain and dyspepsia associated with administration of valdecoxib in the 10 to 20 mg dose range. At doses of valdecoxib higher than 40 mg these differences became insignificant.

- In the [redacted] trials no differences were apparent in the incidence of common GI adverse events (abdominal pain, nausea and vomiting) leading to withdrawal. In these trials the incidence of adverse events associated with non-selective NSAIDs ranged between 0 and 1%.

- A time to event analysis of moderate to severe abdominal pain, dyspepsia and nausea in the 12 week controlled arthritis trials (studies 048, 049, 053, 060 and 061) revealed that, as a composite, the incidence of these symptoms was not different than that associated with placebo and was lower than the incidence associated with non-selective NSAIDs (see Figure 5).

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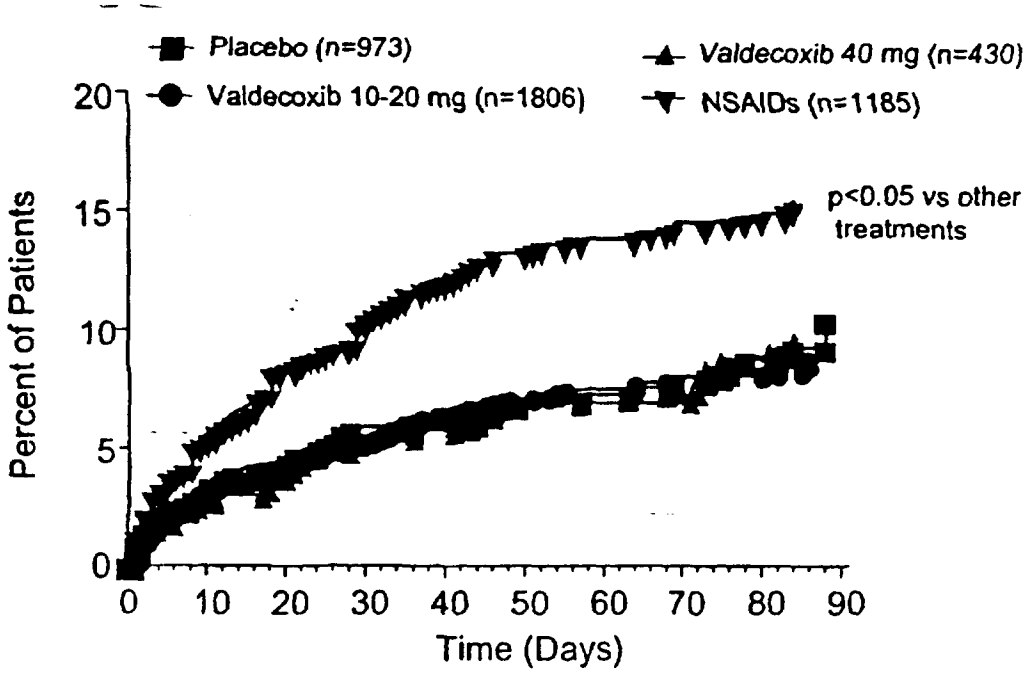
Figure 5

Moderate to Severe GI Adverse Events in the 12-Week Controlled Arthritis Trials[a]



[a] moderate to severe abdominal pain, dyspepsia, nausea

- The incidence of these symptoms continued to increase during the 12 week period of treatment such that a time dependent resistance to side effects was not observed either in the valdecoxib or non-selective NSAID treatment arms.

Serious Gastrointestinal System Adverse Events

As previously mentioned, serious gastrointestinal system adverse events (SAEs) associated with gastro- duodenal ulcer complications were apparent in the vandecoxib controlled arthritis trials, the high dose osteoarthritis and rheumatoid arthritis trial (study 047), and the long-term open label trials. SAEs with a probable or uncertain relationship to study medication are listed in Tables 16, 17, 18 and 19.

TABLE 16

GI-Related Serious Adverse Events with an Uncertain or Probable Relationship to Study Medication Occurring During Treatment or Within 30 Days After Last Dose of Study Medication: Controlled Arthritis Trials

Study/Patient ID/Treatment	Age/ Sex	Day of Onset	Day of Resolution	Preferred Term	Severity	DER Number
015/US0032-0450 PBO	54/M	30	33	Abdominal pain	Mod/Uncertain	971222-CL326
015/US0033-0462 NAP	62/M	10 10	10 (O) 10 (O)	Gastric Ulcer† Gastritis†	Severe/Probable Severe/Probable	971212-CL430
048/US0038-0231 DIC	59/F	47	50	Pancreatitis	Severe/Uncertain	990715-CL929
048/US0046-1154 DIC	71/F	23 25	25 28	Abdominal pain† Gastritis	Severe/Uncertain Mild/Uncertain	991102-CL242 000218-CL193
048/US0051-1118 DIC	62/F	70 70	73 73	Diarrhea† Hematochezia†	Severe/Probable Severe/Probable	991215-CL470
049/US0010-0173 V10	78/F	68	74	Nausea†	Mod/Uncertain	990820-CL716
049/US0108-0427 NAP	50/F	37 40	39 40 (O)	Chest pain non-cardiac Abdominal pain†	Mod/Probable Mod/Probable	990817-CL537
060/US0120-1511 V20	73/F	9 9 9	15 15 15	Ileus† Nausea† Vomiting†	Severe/Uncertain Severe/Uncertain Severe/Uncertain	000210-CL621
061/US0115-1454 NAP	52/M	53 53	55 55	Gastric Ulcer GI Hemorrhage†	Severe/Probable Severe/Probable	000419-CL479
061/US0113-1455 V40	62/F	46 49	46 49 (O)	GI Hemorrhage† Anemia†	Severe/Probable Severe/Probable	000502-CL414

Derived from Appendix 2.1.1. †Patient prematurely withdrew due to this adverse event. Mod; moderate; PBO, placebo; NAP, naproxen sodium; DIC, diclofenac; V10, valdecoxib 10 mg total daily dose; V20, valdecoxib 20 mg total daily dose; V40, valdecoxib 40 mg total daily dose; O, ongoing.

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TABLE 17

GI-Related Serious Adverse Events with an Uncertain or Probable Relationship to Study Medication Occurring During Treatment or Within 30 Days After Last Dose of Study Medication: High-Dose OA and RA Trial

Study/Patient ID/Treatment	Age/ Sex	Day of Onset	Day of Resolution	Preferred Term	Severity/ Relationship	DER Number
047/US0129-2724 NAP	65/F	69 77 80 80	79 (O) 79 (O) 80 (O) 80 (O)	Nausea[†] Vomiting[†] Gastroenteritis Renal Failure Acute	Mod/Probable Mod/Probable Severe/Probable Severe/Probable	000509-CL720 000517-CL629
047/US0217-0962 NAP	71/M	19 19	21 19 (O)	Duodenal Ulcer Hemorrhagic[†] Anemia[†]	Severe/Probable Severe/Probable	000103-CL895
047/US0228-0752 NAP	51/F	14 18	26 26	Melena[†] Abdominal Pain[†]	Severe/Probable Severe/Probable	000907-CL491
047/US0230-1142 V80	52/F	46	47	GI Hemorrhage[†]	Severe/Probable	000413-CL960
047/US0287-0368 NAP	77/M	25	51	Duodenal Ulcer	Severe/Probable	991202-CL934
047/US0304-2585 V80	73/M	29 29 31	38 38 56	Esophagitis[†] Anemia[†] GI Hemorrhage[†]	Severe/Probable Severe/Uncertain Severe/Probable	000202-CL012
047/US0221-0650 NAP	41/M	5 5 5 5 5	6 6 ongoing 6 6	Abdominal pain[†] Hematemesis[†] Hemoccult positivity[†] Nausea[†] Vomiting[†]	Severe/Uncertain Mod/Uncertain Mod/Uncertain Severe/Uncertain Severe/Uncertain	991118-CL150
047/US0304-2656 NAP	82/F	14	48	Gastroesophageal Reflux	Mild/Probable	000225-CL384

Derived from Appendix 2.1.1. [†]Patient prematurely withdrew due to this adverse event. Mod, moderate; NAP, naproxen sodium; V40, valdecoxib 40 mg total daily dose; V80, valdecoxib 80 mg total daily dose; O, ongoing (on date of last dose)

TABLE 18

GI-Related Serious Adverse Events Related With an Uncertain or Probable Relationship to Study Medication That Occurred During Treatment or Within 30 Days Posttreatment: Long-Term Open-Label Trials

Study/ Patient ID/ Treatment	Age/ Sex	Preferred Term	Day of Onset	Day Resolved	Severity/ Attribution	DER #
031/00120055/ V10	69/F	GI hemorrhage (w/d)	54	56	Severe/uncertain	990414-CL859
031/00140006/ V20	57/M	Anemia Diverticulosis (w/d) Duodenitis GI hemorrhage	152 152 152 152	158 158 158 158	Severe/uncertain Severe/uncertain Severe/uncertain Severe/uncertain	990628-CL798
031/00160029/ V20	55F	Gastric Ulcer (w/d)	216	236	Severe/uncertain	991011-CL160
031/00220014/ V20	79/M	Gastritis (w/d) Diverticulitis	137	137	Severe/uncertain Severe/uncertain	990623-CL547
076/02290464/ V80	58/M	Gastric Ulcer (w/d) Hemorrhagic	89	96	Severe/Probable	000713-CL562
061/05051087/ V40	73/F	Gastritis (w/d) Duodenal Ulcer	65	83 (O)	Mod/uncertain Mod/uncertain	000627-CL886
061/05280925/ V20	56/M	Gastritis	18	22	Severe/uncertain	000207-CL964

Data derived from Appendix 2.2.1. w/d – indicates event caused premature withdrawal from the study, (O) ongoing (on date of last dose).

TABLE 19

GI-Related Serious Adverse Events with an Uncertain or Probable Relationship to Study Medication Occurring During Treatment or Within 30 Days After Last Dose of Study Medication: [redacted] Analgesia Trials

Study/Patient ID/Treatment	Age/ Sex	Day of Onset	Day of Resolution	Preferred Term	Severity/ Relationship	DER Number
011/US0002-0105 Oxy/APAP	42/F	2	9	Ileus	Severe/Uncertain	991102-CL030
011/US0002-1010 Oxy/APAP	46/F	2	4	Ileus[1]	Severe/Uncertain	000119-CL708
011/US0002-1012 PBO	63/F	2	8	Ileus	Mod/Uncertain	000328-CL063
038/US0007-0155 V40	75/F	2	5	GI hemorrhage	Mild/Uncertain	000522-CL609
051/FI0001-0330 PBO	59/F	7 7	17 17	Intestinal perforation Peritonitis	Severe/Uncertain Severe/Uncertain	000518-CL899
052/SP0004-0221 PBO	45/M	1	2	Vomiting	Mod/Probable	000419-CL364

Derived from Appendix 2.1.1. [1]Patient prematurely withdrew due to this adverse event. Mod; moderate; Oxy/APAP, oxycodone 10 mg/acetaminophen 1000 mg; PBO, placebo; V40, valdecoxib 40 mg total daily dose.

As shown in these Tables SAEs occurred during treatment or up to 30 days after the last dose. In the controlled arthritis trials a single case of GI hemorrhage associated with valdecoxib treatment was attributed to diverticulosis and angiodysplasia. Although none of the 3,544 patients treated with valdecoxib in the controlled arthritis trials (dose range between 1 and 40 mg per day)

developed serious gastrointestinal hemorrhage only 1/1,347 patients treated with non-selective NSAIDs (active comparator) developed this adverse event. This rate (less than 0.1%) is lower than the expected incidence associated with serious GI hemorrhage associated with non-selective inhibitors in a vulnerable patient population. It can be inferred that most patients who were enrolled in the controlled arthritis trials were not at high risk to develop NSAID induced upper GI hemorrhage..

In the high dose OA and RA trial (study 047) in which patients were treated for 26 weeks with valdecoxib 40 or 80 mg daily, or naproxen 500 mg BID (approximately 400 patients per treatment arm) two patients who were treated with valdecoxib 80 mg developed severe GI hemorrhage. These events were described as probably related to study medication and led to early withdrawal from the study. In the naproxen treatment arm two patients also developed severe GI bleeding and a third developed duodenal ulcer. Based on these results it appears that daily administration of 80 mg of valdecoxib is associated with a significant incidence of GI hemorrhage in an outpatient population treated for osteoarthritis and rheumatoid arthritis. This incidence does not appear to be substantially different than the incidence associated with the administration of naproxen.

Not surprisingly, in the long term trials, gastroduodenal ulcers and/or mucosal damage associated with GI hemorrhage were linked to the use of valdecoxib ranging in daily doses between 10 mg and 80 mg. There did not appear to be a relationship with duration of therapy. Although 6/7 cases were labeled as having uncertain attribution to the study drug, without a comparator arm attribution of these cases to study drug cannot be ruled out.

In the list of SAEs associated with treatment in [redacted] analgesia trials only one case of GI hemorrhage was associated with the use of valdecoxib (40 mg daily). It is notable that there was an absence of cases of GI hemorrhage or upper GI serious adverse events associated with the use of a nonselective NSAID comparator. These findings suggest that the patients who were studied did not manifest vulnerability to NSAID-linked ulcer complications.

Another source of serious gastrointestinal adverse events linked to valdecoxib treatment is study 035 [redacted]

TABLE 20

ANALGESIA STUDIES: (Continued)

Report No.: Protocol No.: Short Title: Location (Volume/Page)	Investigator(s): Study Site: Start Date: Published Study Reference:	Study Design*	No. of Subjects: Age: Range: Sex: Race:	Diagnosis and Criteria For Inclusion	Tested Agent(s) Name: Dosage: Form: Strength: Route of Administration	Regimen: Duration of Treatment	N
8. P: E91-99-02-052 R: E91-00-08-052	10 investigators at 10 European sites 10 December 1999	Multicenter Multi-dose Randomized Double-blind Single dose Comparator- and Placebo-- controlled Parallel group	269 Randomized 269 Dosed 18-88 years 243 male 26 female 269 Caucasian	Patients who have undergone total	Valdecoxib 20 mg tablets Valdecoxib placebo Diclofenac 75 mg SR capsules Diclofenac placebo Oral administration	Valdecoxib 20 mg BID Valdecoxib 40 mg BID Diclofenac 75 mg SR BID Placebo 36 hours	68 69 65 67
9. P: N91-99-02-072 R: N91-00-08-072	Four investigators at four study sites within the United States 26 October 1999	Multicenter Single dose Multi-dose Randomized Double-blind Comparator- and Placebo-- controlled Parallel group	201 Randomized 201 Dosed 20-78 years 30 Male 171 Female 162 Caucasian 28 Black 11 Hispanic 2 Asian 1 other	Patients with	Valdecoxib 20 mg IR tablets Valdecoxib placebo Oxycodone 5 mg / acetaminophen 500 mg capsules (Tylox®) Tylox® placebo Oral administration	Day 1 - Single dose of one of the below: Valdecoxib 40 mg Oxycodone 10 mg/acetaminophen 1000 mg (Tylox®) Placebo Days 2-4, active medication dose Q4-6h PRN (up to 80 mg daily for Valdecoxib) Valdecoxib 40 mg Oxycodone 10 mg/acetaminophen 1000 mg (Tylox®)	68 66 69 80 42

The sponsor has pointed out that in two of these cases *H. pylori* colonization was detected. It should be emphasized that the presence of this organism does not exclude that treatment with the COX-2 inhibitor was a cause for both the formation of peptic ulcerations/ lesions and the subsequent complications described above. At this time there are insufficient data to determine whether *H. pylori* infection increases the risk for complicated GDUs in these patients.

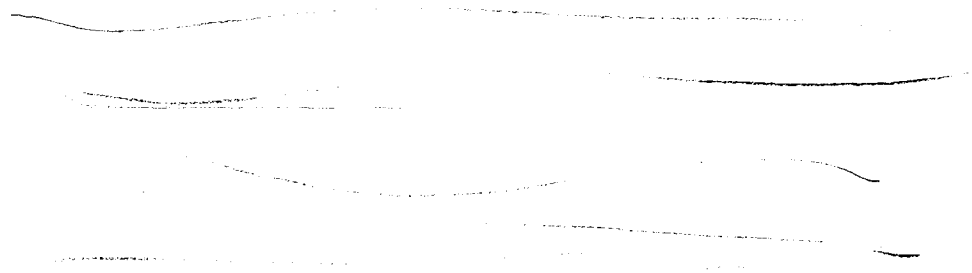
REVIEWER'S COMMENTS

Many of the issues that surround GI safety of valdecoxib, a second generation COX-2 inhibitor, are identical with questions that have previously been raised in an analysis of the first generation COX-2 inhibitors, celecoxib and rofecoxib. It is essential that the Agency take a unified position addressing these issues in order to establish consistent guide posts for informative study designs and labeling of members of this drug class. Significant issues that should be addressed include the following:

- In demonstrating enhanced GI-safety profile COX-2 inhibitors compared to non-selective NSAIDs the sponsor has emphasized that the incidence of endoscopic ulcers/erosions measured during scheduled endoscopies is a safety endpoint. It is not clear that this surrogate measure can be used as a predictor of risk for the development of complicated and/or symptomatic ulcers which occurred at a lower frequency in predisposed individuals who manifest confounding risk factors (see above). The finding of endoscopic ulcers at a scheduled endoscopic examination (defined by the sponsor as endoscopically detected breaks in the mucosa $\geq$3 mm in diameter) has yet to be validated as a surrogate marker for clinically significant adverse events in individuals with low/high risk to develop complications or symptomatic ulcers. Since the natural course of most erosions/superficial small ulcers is characterized by transience and resolution of the mucosal injury, it is critical to know whether the incidence of gastroduodenal ulcers destined to become "bad actors" is impacted by the use of COX-2 inhibitors such as valdecoxib. There is a need to distinguish whether COX-2 inhibitors only have an impact on the incidence of mucosal injury associated with a clinically insignificant course or whether they affect the subset of individuals with lesions predisposed to clinical complications. In the case of celecoxib, the sponsor performed the CLASS study (see above). Unfortunately, although there was a trend in favor of the celecoxib treatment arm, the primary efficacy endpoint (incidence of complicated ulcers) did not achieve statistical significance. An analysis of the incidence of symptomatic and complicated ulcers (a non-prespecified composite endpoint) was carried out. The differences between celecoxib and nonselective NSAID treatment arms were inconsistent and depended on the specific nonselective NSAID comparator. Importantly, the study design did not allow for prospective assignment of risk for complicated ulcers or the composite of symptomatic and complicated ulcers in specific subsets of patients who were predisposed to complications. In the case of patients who were taking low dose aspirin, concomitant usage with celebrex increased the rates of complicated and symptomatic ulcers. In this group, celebrex did not offer an advantage over nonselective NSAIDs. Indeed, when compared to ibuprofen it may have conferred an increased risk for toxicity. With this overview the value of gastroduodenal ulcer incidence measured during scheduled endoscopies as a reliable surrogate measure has been called into question. At this time there are insufficient data to determine whether there is a reduction in the risk to develop complicated and complicated and symptomatic ulcers when the COX-2 inhibitors are compared to nonselective NSAIDs. Labeling that establishes this disclaimer and which avoids disproportionate prominence of results of ulcer measurements (most are asymptomatic) during scheduled endoscopies should be pursued with the sponsor.

- A significant limitation of the information provided in the NDA database is the under-powering of safety outcomes of individuals who may be predisposed to serious adverse events and complications associated with NSAID treatment. Co-therapies or co-morbid conditions that may increase the risk of complicated ulcers patients treated with valdecoxib include the history of prior gastroduodenal ulcers and GI bleeding, treatment with corticosteroids, anti-coagulants or other NSAIDs, old age, debilitated health status, major surgery and extended duration of treatment. Sufficient powering to study each of the aforementioned subsets is not a characteristic of the safety studies that have been provided. In the case of the endoscopic ulcer studies of geriatric subjects age 65 to 75 years treated with valdecoxib study 045 was completed. This study was limited by the fact that only 62 subjects were included in each treatment arm. In the case of the 12 to 26 week controlled arthritis trials only 2/1347 patients treated with non-selective NSAIDs developed clinically significant ulcer complications. This low incidence (0.15%) suggests that a patient population not prone to these complications was studied. These deficiencies can only be remedied by sufficiently powered safety studies. The study population should consist of patients who are at increased risk to develop complicated ulcers.

- An upper limit of 7 days was adhered to in all of the endoscopic studies of healthy subjects treated with valdecoxib (studies 017, 044, 045). Although in some of the PK studies apparently healthy subjects were exposed to longer duration of treatment, small numbers of individuals were enrolled. Therefore, at this time there are no data to assess the ulcerogenic potential in healthy subjects of continued treatment with valdecoxib beyond 7 days.



- The patient population was particularly vulnerable to ulcer complications because it included geriatric subjects up to the age of 76 years. In addition, study enrollees were physiologically stressed as a result of [redacted]
Despite the fact that in some cases ulcer complications occurred during the valdecoxib phase of treatment, a significant contribution of paracoxib administered at the earlier phase must be assumed. Therefore, it can be concluded that in contrast to the minimal risk of valdecoxib treatment in healthy subjects, use of this agent as an analgesic in a physiologically stressed patients who have [redacted] uch as [redacted] appear to be linked to a higher risk for the development of serious adverse complications associated with gastroduodenal ulcers. This risk may be amplified in patients who are predisposed to the development of such complications.

- The sponsor has provided a 7-point scale that quantitates petchiae/erosions/ulcers as measures in the endoscopy studies comparing effects of valdecoxib and other non-NSAID agents. The clinical relevance of this scale, considered a bioassay, which is heavily weighted toward superficial non-ulcer lesions, is dubious.

- As noted by the sponsor, abdominal pain leading to early withdrawal from studies was prevalent in all NSAID treatment arms, including the valdecoxib treatment arms. Although pain occurred with a similar frequency in the placebo treatment group, a correlation of valdecoxib-induced gastroduodenal symptomatic ulcers cannot be made in patients who did not undergo endoscopy. At this time the rate of gastroduodenal ulcers in patients who developed abdominal pain during analgesic trials is not known. This should be stated in the labeling.

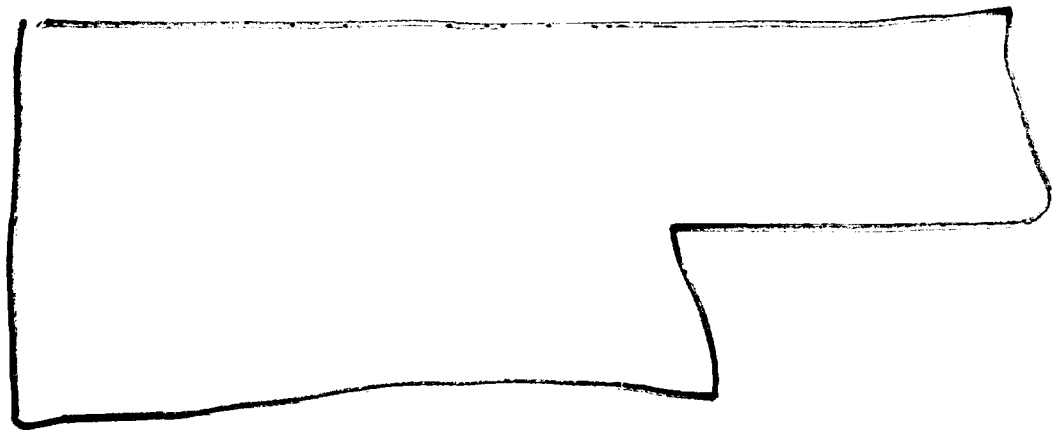
- The interplay between *H. pylori* colonization/infection and valdecoxib in the causation of gastroduodenal ulcers is unknown. This should be stated in the labeling.

- The safety effects of combined aspirin or other non-selective NSAIDs and valdecoxib treatment in patients susceptible to complications of gastroduodenal ulcers have not been adequately assessed. As in the case of celecoxib, the concomitant use of ASA or other nonselective NSAIDs appeared to reverse, at least partially, any potential safety benefit of valdecoxib and may in fact have a potentiating effect on mucosal toxicity. The labeling should caution against concomitant use of ASA or other non-selective NSAIDs with valdecoxib in patients who are susceptible to the development of complications associated with gastroduodenal ulcers.

- The likelihood that COX-2 inhibitors do not appear to provide protection against cardiovascular/thrombotic safety events and/or in some cases increase the risk for these events suggests that an adequately powered study be performed to establish comparative overall safety and mortality of users of valdecoxib alone, low dose ASA alone, and the combination. In the controlled studies of OA and RA patients treated 12-26 weeks only 14% (n=470) of the valdecoxib treated patients (n=3359) were concomitantly treated with low dose ASA. The need for a sufficiently powered hazard analysis is especially important in geriatric patients who are prone to cardiovascular/thrombotic events.

- Some of the issues raised by this review can only be addressed in future studies that enroll larger numbers of patients at risk for the development of gastroduodenal ulcer complications. Studies to evaluate the risk in each of these subsets treated with valdecoxib should be planned as part of a Phase IV commitment.

1 page(s) of revised draft labeling has been redacted from this portion of the review.



Mark Avigan, M.D., C.M.

cc:
HFD-180/V Raczkowski
HFD-180/JKorvick
HFD-180/HGallo-Torres
HFD-180/MAvigan
HFD-181/Consult File

APPENDIX 1

Controlled Arthritis Trials

Study N91-99-02-047
Patient 0207-0211 was a 71 year old female with a history of depression, atherosclerotic cardiovascular disease, cerebrovascular ischemia, chronic obstructive pulmonary disease, asthma, gastrointestinal associated NSAID intolerance, urinary tract infection, renal calculi, hypothyroidism, and OA. Concomitant medications included conjugated estrogens, levothyroxine, citalopram, aspirin, acetaminophen, salmeterol, fluticisone, and ipatropium/albuterol. The patient was randomized to valdecoxib 40 mg BID.

After 23 days of treatment the patient began experiencing dyspepsia which was relieved by eating. The patient also reported epigastric pain and mild nausea. Laboratory examination on Study Day 43 revealed a hemoglobin of 13.6 g/dL compared with a Baseline hemoglobin of 14.3 g/dL and a hematocrit of 41% compared with a Baseline hematocrit of 45%. Stools were found to be hemoccult negative on Study Days 87 and 89 but were Hemoccult positive on Study Day 88. Follow-up laboratories revealed a further drop in hemoglobin and hematocrit to 12.9 g/dL and 40% respectively on Study Day 99. An endoscopy was performed on Study Day 103 revealing a 3.5 cm antral ulcer, gastritis, and duodenitis. Study medication was discontinued on Study Day 103 and the patient was withdrawn from the trial. This event was classified as: **gastric ulcer, GI bleed (1D1).**

Study N91-99-02-047
Patient 0275-1227 was a 48 year old female with a history of hypertension, hiatal hernia, mild gastritis, duodenitis, hysterectomy, facial cellulitis, and RA. Concomitant medications included acetaminophen, prednisone, hydroxychloroquine, and nifedipine. The patient was randomized to valdecoxib 20 mg BID.

After 43 days of treatment the patient began experiencing multiple black, watery stools. Laboratory evaluation on Study Day 45 revealed a hemoglobin of 9.1 g/dL compared with a Baseline hemoglobin of 12.4 g/dL and a hematocrit of 28.0% compared with a Baseline hematocrit of 35.0%. Stools collected on Study Days 51, 52 and 53 were hemoccult negative. Study medication was discontinued on day 56. An endoscopy was performed on Study Day 63 revealing two 0.8 cm and one 0.5 cm duodenal bulb ulcers. A biopsy for *Helicobacter pylori* was classified as: **duodenal ulcer, GI bleed (1C).**

Study N91-99-02-047
Patient 0260-0357 was a 86 year old female with a history of anxiety, depression, otitis media, bilateral cataracts, bilateral macular degeneration, labil blood pressure, hysterectomy, periperal vascular disease, left femoral-popliteal bypass surgery, right bundle branch block, angina, peripheral edema, hyperlipidemea, pneumonia, bronchitis, occult GI bleeding, constipation, abdominal pain, cholecystectomy, colon polyps, esophagitis with stricture formation, bursitis,

compression fracture of T11 and T12, and OA. Concomitant medications included alendronate, alprazolam, and aspirin. The patient was randomized to valdecoxib 20 mg BID.

After 29 days of treatment the patient began experiencing epigastric pain. Stool on Study day 31 was hemoccult positive. An endoscopy was performed on Study Day 31 revealing a mildly edematous pylorus and two distal duodenal bulb ulcers measuring 0.5 cm and 1.0. The smaller of the two ulcers had a base consisting of exudative material and dried blood and the larger of the ulcers was causing some post bulbar stenosis preventing further passage of the endoscope. A biopsy for *Helicobacter pylori* was negative as was a Baseline serology. Laboratory evaluation on day 35 revealed a hemoglobin of 9.7 compared with a Baseline hemoglobin of 16 g/dL and a hematocrit was 29.0% compared with a Baseline hematocrit of 136.0%. Study medication was discontinued on day 29 and the patient was discontinued from the study on day 35. This event was classified as: **duodenal ulcer; GI bleed (1D1).**

Study N91-99-02-047
Patient 0225-0323 was a 67 year old male with a history of tympanoplasty, sciatica, sinus bradycardia, hyperlipidemia, hiatal hernia with surgical repair, ileal ulcers, hemorrhoids, constipation, colonic polyps, GERD, gastroduodenal ulcers, NSAID intolerance, cholcystectomy, and OA. Concomitant medications included glucosamine, garlic, ginko biboba, saw-palmetto, vitamins E and C, simvastatin, atorvastin, famotidine, atenolol, cyclobenzaprine, diflorasone diacetate, and aspirin. The patient was randomized to valdecoxib 40 mg BID.

After 117 days of treatment the patient began experiencing intermittent dyspepsia which was relieved by eating. The patient completed the study and took the last dose of study medication on Study Day 161. The patient had not reported the dyspepsia until day 162. An endoscopy was performed on day 162 revealing a deep 1.2 cm ulcer on the lesser curvature of the antrum with visible blood present, and 6-10 erosions in the duodenal bulb. A biopsy for *Helicobacter pylori* was negative as was a Baseline serology. Blood work on the day of the endoscopy revealed a hemoglobin of 13.6 g/dL compared with a Baseline hemoglobin of 13.7 g/dL and a hematocrit of 39.0% compared with a Baseline hematocrit of 38.0. This event was classified as: **gastric ulcer; GI bleed (1B).**

Study N91-99-02-049
Patient 0092-0070 was a 44 year old female with a history of chronic reflux esophagitis, pyloric erosion, gastroduodenal ulcers, hysterectomy, bladder repair, osteoporosis and OA. Concomitant medications included estropipate, calcium, and halibut liver oil. The patient was randomized to valdecoxib 10 mg QD.

After 15 days of treatment the patient was found to have a decreased hemoglobin and hematocrit. Specifically, the hemoglobin was 13.0 g/dL compared with a Baseline of 14.6 g/dL and the hematocrit was 37.0% compared with a baseline of 43.05. On study day 17 the patient reported nausea and study medication was discontinued. A follow-up laboratory evaluation on study day

19 again revealed a hemoglobin of 13.0 g/dL with a hematocrit of 38.0%. A stool sample collected on day 19 was Hemoccult positive. On study day 23 a physical examination revealed both epigastric and right upper quadrant tenderness. On study day 29 an endoscopy was performed revealing a normal esophagus, 2 -5 petechiae, 2-5 antral erosions, a 0.5 cm antral ulcer with surrounding edema, and a normal appearing duodenal bulb and descending duodenum. A biopsy for a CLOtest was negative. The patient was withdrawn from the study. This event was classified as: **gastric ulcer, GI bleed (1D1).**

APPEARS THIS WAY
ON ORIGINAL

Agent: Valdecoxib
Indication: Analgesia, Dysmenorrhea Osteoarthritis, and Rheumatoid Arthritis
Reviewer: Kent Johnson, MD
Date: November 7, 2001
NDA: 21,341

OUTLINE

APPEARS THIS WAY
ON ORIGINAL

EXECUTIVE SUMMARY

1-RECOMMENDATIONS

A. Approval for the indications of osteoarthritis and rheumatoid arthritis at a dose of 10 mg/day and dysmenorrhea at a dose of 20-mg bid as needed.

B. Nonapproval of the acute pain.

. The extensive safety database at 10-80mg daily in the arthritis safety database is adequate to support approval of the chronic therapy at 10 mg/day for arthritis and acute dose of 20 mg bid for short term use in dysmenorrhea.

2-SUMMARY OF CLINICAL FINDINGS

a) Adequate efficacy has been demonstrated in osteoarthritis and rheumatoid arthritis at 10mg/d with no additional efficacy at 20mg/d.

The safety profile with chronic use in RA and OA is adequate at 10mg/d. At higher total daily doses, the findings of more hypertension and edema are frequently reproduced, and they are formally affirmed in a prospective manner in Trial 47, which directly tested the hypothesis of renal safety at 40 and 80 mg/day. In the analysis of older subpopulations over the age of 65 years edema and hypertension appear to be greater at 20 mg/day compared to 10 mg/ day.

b) Single-dose analgesia has been demonstrated at 20mg and 40mg in the dysmenorrhea, with supportive data from other

c)

d) **Three studies of [redacted] were submitted [redacted].**

e) **No efficacy advantage was demonstrated or suggested for valdecoxib compared to:**

i. **ibuprofen, naproxen [redacted]**
ii. **naproxen, ibuprofen or diclofenac in osteoarthritis studies**
iii. **naproxen in rheumatoid arthrits studies**

3-OVERVIEW OF CLINICAL PROGRAM

ANALGESIA: This NDA consists of a program of analgesia trials to support a claim for acute pain, and a number of trials in osteoarthritis and rheumatoid arthritis to support a claim for chronic use in these conditions. The analgesia program tended to follow drug development programs for acute pain used in the past, relying heavily on single-dose demonstrations of efficacy compared to placebo and active controls, plus PK support demonstrating blood level stability over time and a satisfactory chronic risk/benefit from different indications (osteoarthritis and rheumatoid arthritis) to then *extrapolate* the safety for multiple-dose use in acute pain. The following is the sponsor's request for claims:

> ***An indication for the treatment of acute pain and dysmenorrhea at 40mg/d, with an additional 40mg on day one if needed, and an indication for chronic treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis at a dose of 10mg/day, with the proviso that "some may receive additional benefit at 20mg/day."***

It should be noted that there was the usual interaction with the sponsor regarding the scope and content of their development program. These interactions were more prescriptive in the case of OA and RA, as RA had been recently addressed in a Guidance Document, and the former had been the topic of a number of public meetings during which certain fundamentals such as trial duration, primary endpoints, and statistical methodology, were established. Thus, there was a priori agreement regarding data assessment in OA and RA, but the same cannot be said of analgesia. The agency, in collaboration with outside bodies, has been and remains in the process of formulating current analgesia guidelines, and, in particular, the nature of the evidence base needed to demonstrate efficacy in analgesia. A weakness in the approach used in the past is the extrapolation needed to assert multiple-dose efficacy, rather than having data directly supporting this. In the past, this approach, although not ideal, was deemed acceptable given that agents were drugs which were administered orally and usually showed identical dosing in both the analgesia and arthritis settings. Furthermore, pharmacokinetic paramerters would suggest higher rather than

lower levels on remedication in the acute multi-dose setting. In addition, in many to most acute pain settings, pain intensity typically diminishes rather than increase over time (suggesting that analgesia that is documented to be effective at the time of maximum pain would continue to be adequate as time passed.
An area where extrapolation cannot be made is in the assessment of dosing interval. Single dose efficacy data alone is less robust than comparative multi-dose data in assessing the optimal dosing interval. Although the division is exploring approaches which yields direct multiple-dose evidence and so depends less on extrapolation, the interactions for this NDA preceded this, so in this review the single-dose to multiple-dose extrapolation will be accepted.

The analgesia program consisted of nineteen trials – sever , two dysmenorrrhea, and ten in variou settings. Only four were designed as multiple-dose trials. The other fifteen all were explicitly designed as single-dose,

The dysmenorrhea trials were both 4-part crossover designs. Two rials were designed to test the use of valdecoxib in a nanner, given All trials were both placebo and active controlled except three which were designed to test a ypothesis the nd the two losing studies. The three trials allowed ad lib morphine use in both arms, so, in effect, they employed a "standard-of-care" as the control arm. The inclusion criteria varied widely across these designs, from patients undergoing the standard

This diversity has always been encouraged, as pertinent to any claim is a presumption of generalizability.

. This was an efficacy as well as a safety trial. The "COX-2 hypothesis" relates to organ specific safety; notably the uppergastrointestinal tract. In discussions with the sponsor the division has emphasized the importance of rigorously testing the overall safety as well as upper gastrointestinal safety of valdecoxib. Given the evolving knowledge of selective COX-2 inhibition, this issue is of growing concern. This trial included a pre-defined basket of serious safety endpoints, called clinically relevant adverse events (CRAEs), which were to be formally adjudicated. In addition study 047 included renal safety endpoints in addition to asymptomatic endoscopically ascertained gastroduodenal ulcers as prespecified endpoints

ARTHRITIS: The arthritis program consisted of early dose-ranging RCTs (Trials 15 and 16), followed by four standard efficacy trials (1 hip OA, 1 knee OA, and 2 RA), one active control, non-inferiority trial in OA (trial 63), and four formal safety trials – Trial 47 (OA/RA), 62 (RA), 48 (OA), and 53 (knee OA), all using a similar endoscopic ulcer primary endpoint, and one (47) also using a renal toxicity composite primary endpoint. These safety trials also collected validated efficacy endpoints, although not encompassing the full primary endpoint spectrum needed for formal efficacy evidence in OA or RA.

4-EFFICACY

ANALGESIA: The analgesia trials were assessed by (1) the improvement in pain over time, the $p<0.05$ level, and no adjusting for multiplicity was done.

Using the criteria of replicated success in two of the pain models – dysmenorrhea, and pain, the data support clear single-dose efficacy of .

The clinical relevance of was not adequately demonstrated.

ARTHRITIS: The trials performed for the demonstration of efficacy in RA and OA were conventional and adequate in design. They included three formal efficacy trials in OA (two placebo control trials and one non-inferiority trial using only an active control, and two in RA, both placebo controlled. There were also safety RCTs with safety parameters as primary endpoints that also measured efficacy. These studies employed less standardized athritis efficacy endpoints such as patient and investigator global assessments and time to dropout due to inefficacy.

The analysis of the efficacy results for RA and OA in this NDA were relatively straightforward. Valdecoxib did demonstrate efficacy at the 10mg and 20mg/d dosages in replicated data by usual comparisons with placebo arms, and there were no obvious threats (e.g. a differential dropout pattern) to the validity of these conclusions. Although no formal active control, non-inferiority evidence was pre-specified and pre-agreed upon in this NDA, this NDA, like others in the past, included numerous comparisons with active controls – and these were within the range of what has been seen with prior NDAs. There was no added benefit at 20mg/d, compared to 10mg/d.

5-SAFETY

Note: The review proper contains numerous adverse event tables which are supplied for reference, as the global safety experience of valdecoxib will likely bear critically on approval and labeling. Review comments are made in each section of these databases, but all relevant

safety considerations are captured in the discussions of safety and risk / benefit here in the Executive Summary.

With two notable exceptions – edema and hypertension, valdecoxib was comparable to the standard non-steroidal agents used as active controls in the trials, except for some evidence supporting fewer GI adverse events, and some lessening of opiate side effects (e.g. constipation, dizziness, etc.) in trials with those as active controls. These findings will be reflected in the AE tables in the label. The finding of a greater incidence of edema and hypertension at doses above 20 mg/day, almost uniformly in the databases and clearly when prospectively addressed in formal safety Trials 47 and 62, is of concern, The relationship between these events and the signal of more vascular events at 40mgbid dosing in the predisposed population of Trial [redacted] s unclear. The excess of serious cardiovascular thromboembolic events in the valdecoxib arm of the [redacted] rial (see analgesic safety table #12) is of note as the entire study population received prophylactic low dose aspirin as part of the standard of care in this setting to minimize just such events. Given the emerging concern over a possible pro-thrombotic action of certain agents in the COX2 class, these data are of concern. These findings were seen at high dose in the [redacted] etting, not in the chronic safety studies of similar high doses.

6. DOSING

Valdecoxib should be limited to 10mg/d in chronic use in OA and RA. At this dose the rates of edema and hypertension appear to be similar to the comparator NSAIDs although formal hypothesis testing was not done in this regard. Edema and hypertension appeared increased at higher doses compared to other NSAIDs.

7. SPECIAL POPULATIONS

Analysis of the pivotal RA and OA trials across age (using 65 and 75 as divisors), gender, and race subpopulations did not show any differences by the primary endpoints used in those trials.

REVIEW PROPER

CLINICAL EXPOSURE

The exposure in patient-years for this NDA and 120-Day Update are shown below.

EXPOSURE – ARTHRITIS TRIALS, PATIENT-YEARS

category	valdecoxib (total daily doses)						naproxen	diclofenac	ibuprofen	placebo
	≤5mg	10mg	20mg	30mg	40mg	80mg				
double-blind	106.5	322.7	396.5		315.5	141.5	291.2	248.3	40	161.1
open		308.1	786.8	0.2	736.0	233.4				
total	106.5	584.1	1135.2	0.2	937.7	308.7				

EXPOSURE - [redacted]

Valdecoxib 40mgbid	7.7 patient-years
Placebo	3.7 patient-years

HUMAN PHARMACOLOGY AND PHARMACOKINETICS – See Platelet function: Relevant PK Studies, under Safety (Clinical), and full Pharmacology and Pharmacokinetics Reviews

CLINICAL STUDIES-EFFICACY

The reader is referred to the statistical reviews as well.

PART I: OSTEOARTHRITIS

DATABASE: The osteoarthritis (OA) database shown in TABLE 1 consists of eight randomized controlled trials (RCT), including two pivotal efficacy studies of three months duration. Although the protocols specified numerous primary and secondary endpoints, none addressed the issue of multiple comparison and alpha-spending for statistical inference. Nonetheless, there is widespread agreement that pain, function, and patient global (PG) should be primary domains in short-term OA trials (i.e. less than one year), and here accepted measures in each of these domains are used as primary efficacy endpoints. The fourth endpoint used is trial withdrawal due to inefficacy. As no trial in this application used rescue medication, adjusting for this covariate dose not arise.

In this NDA the three OA primary endpoints for efficacy were captured as (1) pain by 10cm VAS, (2) function by the full Western Ontario and McMasters University Osteoarthritis (WOMAC) Index, and (3) patient global by 10 cm VAS, although the trials collected further efficacy data. Some trials were designed as safety studies with endoscopic and, in some cases, renal endpoints; the results of these are given in the Safety Section of this review. The control arms used were placebo (plc), naproxen (nap), ibuprofen (ibu), or diclofenac (dicl). Patient entry criteria were OA diagnosis by ACR criteria, plus pain of 4.0cm or more on the 10cm VAS and a patient global of "poor" or "very poor," either de novo or after withdrawal of the patient's prior non-steroidal medication ("flare").

TABLE 1: OA database

Trial	duration, size	arms	primary endpoints
Dose-finding trial			
15 knee OA	6wk, ~80/arm	0.5,1.25,2.5,5,& 10bid,10qd,nap,plc	
Efficacy trials			
49 hip OA	3mo, ~120/arm	5, 10, nap, plc	pain, fctn, PG
53 knee OA	3mo, ~200/arm	5, 10, 20, nap, plc	pain, fctn, PG
48 OA*	3mo, ~200/arm	10,20,ibu,dicl, plc	PG, IG, ineff.
63 knee/hip OA** (ongoing)	6mo, ~260/arm	10, 20, dicl	efficacy, JSN
Safety trials			
48 OA (nos)	3mo, ~200/arm	10,20,ibu,dicl, plc	endoscopic ulcer

47 OA/RA	6mo, ~400/arm	20bid,40bid,nap	renal,endos.ulcer
53 knee OA	3 mos ~200/arm	5, 10, 20, nap, plc	endoscopic ulcer

* Trial 48 – Enrolled patients with the diagnosis of OA, not otherwise specified.

** Trial 63 – Six-month efficacy trial, followed by a six-month open extension to assess joint space narrowing (JSN) at 12 months. (Interim report of 6 month data only)

TRIALS 49 AND 53

PATIENT DISPOSITION: Patients were matched across arms by the usual demographic and clinical criteria (TABLE 2, below). Substantial premature patient withdrawal occurred (25 to 50%) over the three-month trial duration, and most dropouts were due to treatment failure. The dropouts for treatment inefficacy or adverse events are shown below; a small number discontinued for other reasons.

TABLE 2: Trials 49 & 53: Patient Disposition

	Enrolled	Completed	Withdrew	
			Rx. Failure	adverse event
Trial 49				
val 5mg	120	73 (61%)	32 (27%)	10 (8%)
val 10mg	111	65 (59%)	31 (28%)	11 (10%)
naproxen	118	71 (60%)	24 (20%)	15 (13%)
placebo	118	49 (42%)	51 (43%)	7 (6%)
Trial 53				
val 5mg	201	162 (81%)	16 (8%)	12 (6%)
val 10mg	206	150 (73%)	24 (12%)	18 (9%)
val 20mg	202	158 (78%	20 (10%)	11 (5%)
naproxen	205	149 (73%)	13 (6%)	26 (13%)
placebo	205	131 (64%)	42 (20%)	17 (8%)

DROPOUT ANALYSES: TABLES 3 and 4 show comparisons of the status of dropouts versus completers by baseline and end-of-trial means and standard deviations (in parentheses) of various factors. The following parameters are presented: age (yr), percent female, disease duration (yr), pain (0-100 for Trial 49, or 0-68 for Trial 53), patient global (% "poor" for baseline, % "poor" or "very poor" for last visit), and function (0-68 for Trial 53 only). Although some parameters are less sensitive than others at showing differences between dropouts and completers, there was no dropout pattern which might compromise the validity of inferences drawn.

TABLE 3: Trial 49 – Comparison of Baseline / End-of-trial Status: Dropouts vs Completers

arm	placebo		val 5mg/d		val 10mg/d		naproxen	
	d/outs	compl.	d/outs	compl.	d/outs	compl.	d/outs	compl.
BASELINE PARAMETERS								
age	67	58	63	59	66	64	61	66
female	72%	63%	66%	68%	61%	69%	70%	68%
d.dur.	6 (7)	6 (7)	5 (6)	7 (8)	7 (8)	6 (5)	5 (7)	6 (5)
pain	72(15)	67(15)	73(15)	73(15)	78(13)	71(15)	68(16)	70(15)
pt glob	77%	90%	87%	88%	80%	89%	91%	92%

Trials 49 and 53 are adequate and well controlled studies confirming the efficacy of valdecoxib 10 mg/ day for the treatment of osteoarthritis. Dose ranging study of valdecoxib 20 mg/day in trial 53 did not support added benefit for this dose although a small numeric advantage at withdrawal due to lack of efficacy was seen at the higher dose (8.7% versus 5.4%).

TRIAL 48.

This trial compared valdecoxib 10mg/d, valdecoxib 20mg/d, ibuprofen 800mgTID, and diclofenac 75mgBID over three months, and it used both endoscopic ulcers and four clinical efficacy parameters (patient and investigator globals, and incidence and time to inefficacy withdrawal) as primary endpoints. It was powered by both endoscopic ulcers rates and the two global measures.

TABLE 6: Trial 48: Patient Disposition

	Enrolled	Completed	Withdrew	
			Rx. Failure	Adverse Event
val 10mg	204	150	16	19
val 20mg	219	165	17	20
ibuprofen	207	156	11	27
diclofenac	212	152	12	34
placebo	210	135	45	15

RESULTS:

TABLE 7: Trial 48: Primary Endpoint Results at 3 Months

	Patient global	Inv. global	Withdrawals	
	(0-4 Likert)	(0-4 Likert)	(incidence)	(time to withdrawal)
val 10mg	3.12 / -0.54*	3.01 / -0.60**	16/204***	***
val 20mg	3.07 / -0.59*	3.01 / -0.58*	17/219***	***
ibuprofen	3.16 / -0.63*	3.11 / -0.61*	11/207***	***
diclofenac	2.98 / -0.65***	2.91 / -0.58***	12/212***	***
placebo	3.12 / -0.42	3.01 / -0.36	45/210	

*, **, *** statistical significance at $p<0.05$, <0.01, and <0.001 levels, respectively, compared to placebo

COMPARISONS TO ACTIVE CONTROLS:

Although no study was designed as a non-inferiority trial and none was powered by an equivalence hypothesis, the sponsor nonetheless calculated the so-called Q-statistic, the ratio of the mean change on the test drug to the mean change on the active control, and its 95% confidence interval. Although this method has mathematical properties which make interpretation impossible as the denominator approaches zero, it offers an additional mathematical comparison of two response rates (RR) expressed as a ratio, RR1/RR2, in addition to a difference, R2-R1, and the 95% confidence interval of this quantity has been used in the past to assess NSAID comparability for approval evidence, although not for an

LAST VISIT PARAMETERS								
pain	74(24)	37(27)	71(23)	42(27)	76(25)	30(28)	70(26)	33(28)
pt glob	63%	6%	66%	15%	65%	10%	57%	15%

TABLE 4: Trial 53 – Comparison of Baseline / End-of-trial Status: Dropouts vs Completers

arm	placebo		val 5mg/d		val 10mg/d		val 20mg/d		naproxen	
	d/out	com	d/out	com	d/out	com	d/out	com	d/out	com
BASELINE PARAMETERS										
age	59	61	57	59	61	61	60	60	60	60
sex	58%	68%	56%	65%	70%	63%	70%	66%	64%	62%
d dur	6 (9)	5 (7)	10(11)	6 (9)	8 (9)	5 (7)	6 (8)	7 (8)	5 (10)	7 (8)
pain	11 (3)	11 (4)	11 (3)	11 (3)	11 (3)	11 (3)	12 (3)	11 (3)	11 (3)	11 (3)
fctn	40(11)	39(12)	39(12)	39(11)	40(11)	39(11)	41(11)	38(11)	39(10)	39(11)
glob	4 (.5)	4 (.4)	4 (.5)	4 (.3)	4 (.5)	4 (.4)	4 (.6)	4 (.3)	4 (.4)	4 (.4)
LAST VISIT PARAMETERS										
pain	11 (5)	7 (4)	11 (4)	6 (4)	11 (4)	7 (4)	11(4)	6 (4)	11(4)	6 (4)
fctn	39(14)	25(14)	37(13)	24(12)	35(14)	24(14)	37(14)	23(13)	35(13)	23(14)
glob	4 (1)	2 (1)	4 (1)	2 (1)	3 (1)	2 (1)	4 (1)	2 (1)	3 (1)	2 (1)

RESULTS: The results of primary endpoint analyses and the analysis of withdrawals for inefficacy, plus their respective confidence interval ranges, are shown in TABLE 5.

TABLE 5: Trials 49 & 53: Primary Endpoint Results at 3 Months

	——————Baseline / Change from Baseline——————			
	Pain	function	Patient global	Inefficacy dropouts
	(0-10 VAS)	(0-68 Likert)	(0-10 VAS)	
1. TRIAL 49				
val 5mg	7.2 / -2.1	54.7 / -12.0* *	4.1 / -1.2 *	32/120 **
val 10mg	7.3 / -2.3 *	52.8 / -14.0 ***	4.1 / -1.3 **	31/111 *
naproxen	6.9 / -2.2	51.8 / -13.8 ***	4.1 / -1.2 *	24/118 ***
placebo	7.1 / -1.5	52.5 / -5.3	4.1 / -0.9	51/118
Trial 53				
val 5mg	7.1 / -3.1	53.0 / -16.8	4.1 / -1.4	12/201 ***
val 10mg	7.2 / -3.0	54.7 / -17.3 *	4.1 / -1.5* *	18/206 *
val 20mg	7.3 / -3.3 *	53.4 / -17.2 *	4.2 / -1.6 **	11/202 **
naproxen	7.2 / -3.2 *	53.7 / -18.0 *	4.1 / -1.4	26/205 ***
placebo	7.1 / -2.6	53.5 / -13.5	4.1 / -1.2	17/205

*, **, *** statistical significance at p<0.05, <0.01, and <0.001 levels, respectively, compared to placebo

Note: Comparisons of dropouts by all causes also showed statistical significance for all active arms in Trial 49, and for the valdecoxib 5mg and valdecoxib 20mg arms in Trial 53.

Conclusion:

explicit equivalence claim. It was found, from analysis of a number of early NSAID NDAs in OA and RA, that approvability in OA correlated with active control trial demonstrations showing the 95% lower bound of the Q statistic usually 0.6 or more for OA , or 0.7 or more for RA. (A 95% upper bound of the Q of less than one means a statistically significant inferiority has been demonstrated.) It is important to note that this statistical model, with the outcomes as noted, was never proposed as an adequate basis alone for evidence of efficacy of new proposed therapy -- randomized evidence from placebo (negative) controlled settings was required. Using this approach one would conclude that all but one of the naproxen comparisons and all of the ibuprofen comparisons were robust, but only two of the four diclofenac comparisons were (see data below).

TABLE 8: Trials 49, 53, and 48: Q-value (95% CI) Comparisons to Active Controls

	comparison	pain	function	pt. global
Trial 49				
	val5mg v nap	0.97(0.67-1.38)	0.65(0.56-1.15)	1.02(0.79-1.30)
	val10mg v nap	1.06(0.75-1.50)	1.04(0.72-1.51)	1.09(0.86-1.40)
Trial 53				
	val5mg v nap	0.98(0.82-1.18)	0.93(0.75-1.15)	0.99(0.85-1.16)
	val10mg v nap	0.96(0.79-1.15)	0.98(0.79-1.21)	1.08(0.93-1.26)
	val20mg v nap	1.03(0.86-1.23)	0.96(0.77-1.19)	1.10(0.95-1.28)
Trial 48		pt. global	inv. global	
	val10mg v ibu	0.98(0.67-1.44)	1.12(0.79-1.60)	
	val20mg v ibu	1.01(0.70-1.49)	1.06(0.75-1.61)	
	val10mg v dicl	0.78(0.55-1.09)	0.93(0.67-1.27)	
	val20mg v dicl	0.80(0.57-1.11)	0.87(0.63-1.20)	

TABLE 9: Trial 63: Patient Disposition

	Enrolled	Completed	Withdrew	
			Rx. Failure	adverse event

val 10mg	259	188	21	19
val 20mg	261	205	22	18
diclofenac	264	187	16	40

TABLE I0: Trial 63: Efficacy Results: P values (1st entry), Q values (95% CI)(2nd entry)

endpoint	val10mg vs diclof	val20mg vs diclof	val10mg vs val20mg
patient pain	0.074, 0.83 (0.67,1.03)	0.169, 0.87 (0.70,1.07)	0.679, 0.96 (0.76,1.20)
patient global	0.051, 0.84 (0.70,1.01)	0.022, 0.82 (0.67,0.98)*	0.728, 1.03 (0.84,1.27)
WOMAC-full	0.006, 0.78 (0.64,0.94)*	0.042, 0.84 (0.69,1.00)	0.481, 0.93 (0.76,1.15)
time-to-rx. failure	0.404	0.472	0.978

* statistically significant, diclofenac superior to valdecoxib

OTHER EFFICACY EVIDENCE

TRIAL 15: This was a six-week dose-response study of valdecoxib at 0.5mgbid to 10mgbid which showed statistically significant improvement in the three primary endpoints at all but the lowest valdecoxib dose.

TRIAL 47: The only other randomized trial in OA with efficacy analyses available was Trial 47, a combined OA/RA trial of renal and GI safety. It employed four pre-defined efficacy endpoints, the patient and investigator global, and the incidence and time-to-dropout for inefficacy. Trial 47 did not use a placebo arm, so no negative control efficacy comparisons could be made, and no statistically significant superiority was show for any pair-wise comparison of active drugs for any of the four endpoints, but this is an insensitive method to detect small differences. As described above, the Q-statistic and its 95% confidence interval offer a method to look in a more discriminating manner for small differences for continuous or interval variables, so this was done for the two global assessments in this trial, showing a Q of 0.73 [ ] for the valdecoxib 20mgbid vs naproxen patient global comparison, and a Q of 0.77 [ ] for the investigator global. For the valdecoxib 40mgbid vs naproxen comparisons the Q's were 0.77 [ ] and 0.86 [ ] for the patient and investigator global, respectively.

CONCLUSION

Efficacy is adequately demonstrated in osteoarthritis for valdecoxib at 10mg/d. No additional evidence was demonstrated at higher doses in placebo or active controlled studies.

PART II: RHEUMATOID ARTHRITIS

DATABASE: The rheumatoid arthritis (RA) database consists of five randomized controlled trials -- one early dose-finding study, two pivotal efficacy studies of three month duration, and two safety studies. Patients were enrolled if they fulfilled ACR diagnostic criteria for RA, and displayed an adequate increase in symptoms ("flare") upon discontinuation of the current anti-inflammatory medication.

(Note: The interesting question as to the relation of the degree of flare, and the relation of the baseline, pre-flare state, to that patient's outcome in the trial, is likely not relevant to the internal validity of these trial and was not explored in the NDA.

The RA efficacy studies used a variety of endpoints, including the traditional ACR20 ("success" being defined as at least 20% improvement in number of tender joints and number of swollen joints, plus a 20% improvement in at least three of the remaining five components: patient global, physician global, pain, acute phase reactant, and a functional measure), and the modified Health Assessment Questionnaire (mHAQ). Since the introduction of the ACR20, multiplicity has not been an issue in short-term RA trials, and, as in OA, no rescue medication was used. The main features of the four RCTs are shown in TABLE 9, with control arms being placebo (plc), naproxen (nap), ibuprofen (ibu), or diclofenac (dicl). Two RA safety trials are shown, which are reviewed in the Arthritis Safety Review.

TABLE 9: RA Database

Trial no.	duration, size	arms	primary endpoints
Dose finding trial			
16	6wk, ~80/arm	0.5,1.25,2.5,5,& 10bid,10qd, nap,plc	ACR20
Pivotal efficacy trials			
60	3mo, ~220/arm	10,20,40, nap, plc	ACR20
61	3mo, ~220/arm	10,20,40, nap, plc	ACR20
Safety trials			
47 OA/RA	6mo, ~400/arm	20bid, 40bid, nap	renal,endos.ulcer
62 RA	6mo, ~240/arm	20, 40, diclof	renal,endos.ulcer

RESULTS

TRIALS 60 & 61

PATIENT DISPOSITION: Patients were matched across arms by the usual demographic and clinical criteria (see below, TABLES 11 and 12). As in OA, there was substantial premature patient withdrawal over the three-month trial duration. Inefficacy or adverse event discontinuations are shown in TABLE 10; a few patients dropped out for other reasons.

TABLE 10: Trials 60 & 61 - Patient Disposition

	enrolled	completed	Withdrew	
			Rx Failure	adverse event
Trial 60				
val 10	209	132 (63%)	49 (23%)	11 (5%)
val 20	212	132 (62%)	48 (23%)	12 (6%)
val 40	221	139 (59%)	56 (25%)	19 (9%)
naproxen	226	137 (61%)	57 (25%)	13 (6%)
placebo	222	92 (41%)	102 (46%)	10 (5%)
Trial 61				
val 10	226	137 (61%)	61 (27%)	10 (4%)
val 20	219	137 (63%)	56 (26%)	12 (5%)

val 40	209	137 (66%)	48 (23%)	13 (6%)
naproxen	219	145 (66%)	43 (20%)	21 (10%)
placebo	220	95 (43%)	92 (42%)	9 (4%)

DROPOUT ANALYSES: TABLES 11 and 12 show comparisons of the status of dropouts versus completers by baseline and end-of-trial criteria. The following parameters are presented: age (yr), percent female, disease duration (yr), percent of patients on steroids and methotrexate (mtx), patient global (% "poor" or "very poor"), median tender joint (TJ, 0-68) and swollen joint counts (SJ, 0-66), and mHAQ (0-3). As in osteoarthritis, certain parameters are much more sensitive to change (e.g. the ACR20 success, the mHAQ, and the patient global), but no dropout pattern is discerned which might compromise the validity of inferences drawn.

TABLE 11: Trial 60 – Comparison of Baseline/End-of-trial Status: Dropouts vs Completers

arm	placebo		val 10mg/d		val 20mg/d		val 40mg/d		naproxen	
	d/out	com	d/out	com	d/out	com	d/out	com	d/out	com
BASELINE PARAMETERS										
age	44	57	55	50	56	54	56	56	58	53
sex	73%	76%	66%	74%	80%	79%	79%	82%	77%	77%
d dur	6	8	7	9	7	7	9	8	8	7
ster	33	39	39	38	39	38	39	34	38	33
mtx	60	49	59	50	57	54	53	50	44	52
pain	69	50	70	65	72	57	56	61	65	53
TJ	24	27	30	27	26	27	27	25	23	24
SJ	1	18	18	17	17	17	19	18	16	19
mHAQ	1.38	1.19	1..63	1.38	1.63	1.38	1.50	1.38	1.50	1.13
LAST VISIT PARAMETERS										
pain	52	7	54	11	59	8	53	7	71	11
TJ	22	7	25	5	22	9	22	7	23	6
SJ	15	6	15	7	14	7	16	7	15	6
mHAQ	1.38	0.75	1.03	0.88	1.50	0.80	1.38	0.88	1.03	0.88
ACR20	20%	67%	24%	63%	20%	64%	15%	64%	12%	60%

TABLE 12: Trial 61 – Comparison of Baseline/End-of-trial Status: Dropouts vs Completers

arm	placebo		val 10mg/d		val 20mg/d		val 40mg/d		naproxen	
	d/out	com	d/out	com	d/out	com	d/out	com	d/out	com
BASELINE PARAMETERS										
age	55	58	56	56	56	58	56	53	61	59
sex	73	82	82	83	75	73	68	79	68	79
d dur	8	9	8	10	7	8	8	8	9	8
ster	35	37	35	35	40	37	42	36	34	31
mtx	47	48	38	56	43	49	43	47	44	50
pain	60	48	64	53	57	47	62	53	60	46
TJ	29	26	28	25	26	27	28	26	28	28
SJ	17	17	19	18	17	18	19	17	19	18
mHAQ	1.50	1.38	1.50	1.25	1.63	1.25	1.50	1.38	1.38	1.14
LAST VISIT PARAMETERS										

pain	49	7	44	10	44	7	35	4	60	11
TJ	25	7	20	8	18	8	18	7	22	12
SJ	14	8	14	8	12	8	12	8	14	6
mHAQ	1.38	0.88	1.50	0.75	1.50	0.75	1.25	0.75	1.38	0.75
ACR20	18%	64%	22%	62%	22%	64%	27%	66%	17%	53%

RESULTS:

TABLE 13: Trials 60 & 61: Primary Endpoint Analyses

	3-mo ACR20 Success	Inefficacy Withdrawals
Trial 60		
val 10	103/209 (49%) ***	49/209 (23%)***
val 20	102/212 (48%) ***	48/212 (23%)***
val 40	102/221 (46%) ***	56/221 (35%)***
naproxen	100.225 (44%) **	57/226 (25%)**
placebo	70/222 (30%)	102/222 (46%)
Trial 61		
val 10	103/226 (46%)***	61/226 (27%)***
val 20	103/219 (47%)**	56/212 (26%)***
val 40	104/209 (50%)**	48/209 (23%)***
naproxen	115/219 (53%) ***	43/219 (20%)***
placebo	71/220 (32%)	92/220 (42%)

*, **, *** statistical significance at $p<0.05$, <0.01, and <0.001 levels, respectively, compared to placebo

Note: Comparison of dropouts from all causes also showed statistical significance for all active treatment arms in both Trials 60 and 61.

For interest, the means and standard deviations of the mHAQ are shown in TABLE 14, and the Q statistic with its 95% confidence interval for active control comparisons of four selected endpoints in TABLE 15. (For a discussion of the Q-statistic, see Comparisons to Active Controls section of Part I: Osteoarthritis, above.) By these data, valdecoxib appears slightly better compared to naproxen in Trial 60 compared to Trial 61, but in neither trial is there much support for a dose-response effect.

TABLE 14: Trials 60 & 61: M-HAQ Results

	Baseline	Change
Trial 60		
val 10	1.3 (0.68)	-0.3 (0.57)***
val 20	1.5 (0.67)	-0.3 (0.51)***
val 40	1.4 (0.69)	-0.3 (0.55)***
naproxen	1.4 (0.69)	-0.3 (0.57)***
placebo	1.4 (0.72)	-0.1 (0.50)

Trial 61		
val 10	1.4 (0.65)	-0.3 (0.52)***
val 20	1.4 (0.68)	-0.3 (0.55)***
val 40	1.3 (0.69)	-0.3 (0.56)***
naproxen	1.4 (0.71)	-0.4 (0.58)***
placebo	1.3 (0.72)	-0.1 (0.49)***

*, **, *** statistical significance at p<0.05, <0.01, and <0.001 levels, respectively, compared to placebo

TABLE 15: Trials 60 & 61 - Q-value (95% CI) Comparisons of Valdecoxib to Naproxen

Trial 60	pt. global	tender joints	swollen joints	mHAQ
val10 v nap	1.02 (0.83-1.15)	0.99 (0.80-1.22)	1.03 (0.83-1.29)	0.97 (0.70-1.32)
val20 v nap	0.91 (0.73-1.13)	0.94 (0.76-1.17)	0.92 (0.75-1.13)	0.84 (0.59-1.17)
val40 v nap	0.94 (0.76-1.16)	1.06 (0.87-1.30)	1.05 (0.87-1.28)	0.89 (0.64-1.23)
Trial 61				
val10 v nap	0.85 (0.65-0.97)	0.84 (0.70-1.01)	0.81 (0.65-0.99)	0.67 (0.47-0.92)
val20 v nap	0.84 (0.68-1.01)	0.82 (0.67-0.99)	0.85 (0.69-1.03)	0.71 (0.51-0.97)
val40 v nap	0.84 (0.68-1.02)	0.97 (0.82-1.16)	0.86 (0.70-1.05)	0.76 (0.55-1.03)

There is no suggestion of added efficacy at 20 mg/day compared to 10mg/day.

OTHER EFFICACY EVIDENCE

TRIAL 16: The dose ranging RA study, Trial 16, failed to demonstrate any statistical separation at 6 weeks for any active treatment arm, including the naproxen control, compared to placebo for the ACR20 endpoint.

TRIAL 47: The only other randomized trial in RA with efficacy analyses available was Trial 47, a combined OA/RA trial of renal/GI safety. It employed four pre-defined efficacy endpoints, the patient and investigator globals, and the incidence and time to dropout for inefficacy. Trial 47 did not use a placebo arm, so no negative control efficacy comparisons could be made, and no statistically significant superiority was show for any pair-wise comparison of active drugs for any of the four endpoints, but this is an insensitive method to detect small differences. As described in the OA Section earlier, the Q-statistic and its 95% confidence interval offer a method to look in a more discriminating manner for small differences for continuous or interval variables, so this was done for the two global assessments in this trial. TABLE 16 displays the Q values for the 614/1218 patient RA subset of this trial, both by all RA patients enrolled with the analysis point being 14 weeks and those enrolled pre-amendment (n=457) using a 26 week point for analysis. (Because of slow enrollment of patients with RA in Trial 47, the protocol was amended to change the RA analysis from week 26 to week 14, allowing enrollment of RA patients for only 14 weeks rather than 26 weeks.)

TABLE 16: Trial 47 Q value comparisons for RA subset

14 wk comparisons		Q (95% CI)